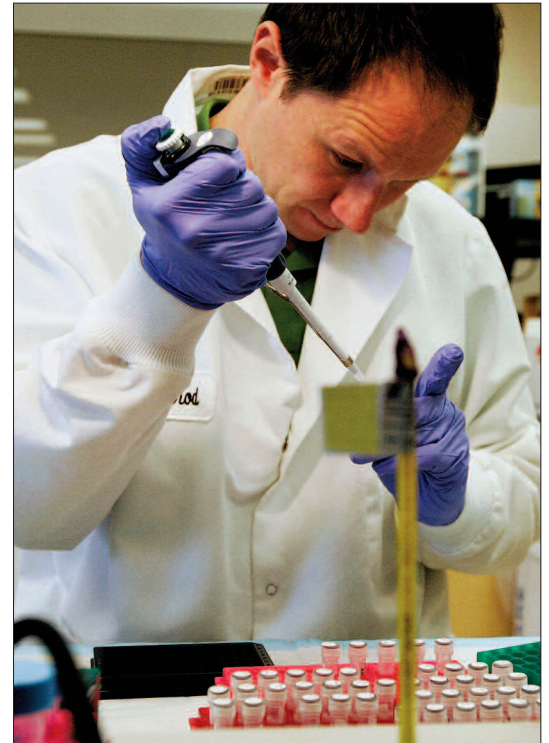


Genes and Health

Is gene therapy for disease on the horizon?

Ever since scientists began to decipher the human genome in the 1990s, hopes have run high that unraveling the genetic code would rapidly revolutionize health care. But while gene research has changed scientists' understanding of many diseases, practical applications remain few. Genetic tests for single-gene diseases such as cystic fibrosis are available, and doctors can more precisely pinpoint the kind of cancer a patient has by analyzing genes. Gene tests can also predict how patients will respond to some drugs. However, no actual gene therapy has been approved for human use, and researchers now know that diseases such as heart disease, Alzheimer's and adult-onset diabetes usually result from a complex interaction among numerous genes and a person's environment. These findings cast doubt on whether current genetic tests for such prevalent diseases are accurate and whether gene science makes it any easier to find treatments.



A technician tests DNA samples at Pathway Genomics, a San Diego maker of direct-to-consumer genetics test kits. Plans to sell the kits at Walgreens drug stores stalled after the Food and Drug Administration questioned their reliability.

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Genes and Health

BY MARCIA CLEMMITT

THE ISSUES

According to the manufacturers' claims, genetic testing kits sold by mail can help consumers diagnose their susceptibility to many common diseases.

But does direct-to-consumer (DTC) home testing really work?

Among the curious was one of the world's preeminent scientists, none other than Francis Collins, director of the National Institutes of Health. In the 1990s and early 2000s, as head of the National Human Genome Research Institute, Collins oversaw the first mapping of the 3 billion-piece puzzle of human genetics.¹

To satisfy his curiosity, Collins conducted his own "undercover" operation in 2009 to check out DTC tests.

Collins submitted his own DNA — using a fake identity — to three companies that sell genetic test kits to consumers who hope to learn about their risk for health conditions such as diabetes and cancer. * The results, he later reported, were mixed. On the positive side, the three detailed maps of Collins' DNA had almost no differences from one another and appeared to be "highly accurate."

* DNA is a large molecule that transmits inheritable traits from generation to generation and carries the blueprints of the cells. An organism's genome is its complete set of DNA — two complementary strands of repeating chemical units called nucleotides, or bases, bound together like a spiral ladder. A gene is any section of DNA that is inheritable as a unit from one's parents and contains the code for creating either a protein or some other molecule that performs a function in the cells.



AP Photo/Monroe Evening News/Katt Lattanzio

The rapid-aging disease progeria afflicts 2-year-old Lindsay Ratcliffe, shown with her father at a Flat Rock, Mich., restaurant in 2006. A gene mutation responsible for the extremely rare disorder — only about 40 to 45 cases are known worldwide — was discovered in 2002 and is helping scientists understand the aging process in general.

When it came to predicting health risks, however, the results were the opposite of clear and consistent.

Labs predict disease risk by scanning an individual's genome in search of points at which the DNA shows small variations from the norm. Some of these variations, known as SNPs (single-nucleotide polymorphisms), occur more often in people who have a particular disease than in those who don't. For virtually any relatively common disease, such as adult-onset diabetes or heart disease, however, numerous SNPs appear to be associated with the condition. Moreover, different people with the disease show different patterns of suspect SNPs. As a result, genetic tests can vary wildly when it

comes to risk prediction, even though each is based on reputable science.

In Collins' case, one company based its risk prediction for a particular disease on five SNPs and pronounced him at low risk; a second, using 10 SNPs, advised him he was at high risk; the third, scanning for 15 SNPs, pronounced his risk average. Collins' conclusion: Personal genomics shows promise but needs substantial work before it's ready for prime time.²

In short, the era of so-called personalized medicine, with clear diagnostics and targeted cures for diseases rare and common, has yet to arrive. In the 21st century, scientists have discovered that the relationship between genes and disease is many times more complex than most imagined. And while knowledge has advanced tremendously, practical applications emerge with agonizing slowness. No true "gene therapy" — using actual genetic material to "repair" someone's

own disease-inducing DNA — has yet been approved by the Food and Drug Administration (FDA), for example.

Nevertheless, there should be no mistaking that the federal Human Genome Project (HGP) has greatly advanced understanding of human biology, says Len A. Pennacchio, head of the Department of Energy's Joint Genome Institute. In a little over a decade, beginning in 1990, the HGP headed by Collins "assembled for the first time the 3 billion puzzle pieces" — molecules called nucleotides — that make up a typical human genome, Pennacchio explains. "Early on, a lot of people doubted that it could be done."

Furthermore, the \$3 billion undertaking revealed that, while all humans

A Glossary of Genetic Terminology

Gene science has its own language, which can make deciphering news articles about genetic medicine a rough road. Here's a guide:

Allele: An alternative form of a gene.

Dark DNA: Parts of the genome that don't carry instructions for producing proteins or other gene products in cells. Once thought to have no purpose in the body, dark DNA is now believed to be vitally involved in regulating how genes are turned on and off.

DNA: Deoxyribonucleic acid; the molecule in cells that carries genetic information and passes it down from parents to children.

Epigenetic change: A change in the way genes are expressed — turned on or off — that occurs without the actual genome sequence being altered. To their surprise, scientists are finding that some epigenetic changes can be passed down from parents to offspring.

Gene: A segment of the genome that carries the code for producing a protein or some other cell product.

Gene expression: When and where genes are turned on and off; patterns of gene expression determine whether a cell is muscle tissue or bone, lungs or liver and also probably help predispose humans to some diseases.

Genome: The entire set of genetic instructions found in each cell.

Genome-wide association study: A branch of genetic research in which scientists scan the genomes of thousands of individuals, looking for genes and gene variations that appear more often in people with a certain disease than in people who don't have that illness.

Genotype: An individual's complete genetic makeup.

Mutation: A change in one's DNA sequence. A mutation in an egg or sperm cell can be passed on to the offspring; a mutation in any other cell cannot. Mutations can be caused by environmental factors, such as ultraviolet light, or can be accidents that occur as DNA copies itself when cells divide.

Nucleotide: The molecular building block of DNA.

Phenotype: An individual's physical characteristics.

Single-nucleotide polymorphism: SNP; a precise spot in the 3 billion-nucleotide genome sequence where the DNA of different people is likely to vary.

Source: W. Gregory Feero, Alan E. Guttmacher, and Francis S. Collins, "Genomic Medicine — An Updated Primer," New England Journal of Medicine, May 27, 2010, p. 2001.

"generally share" the same 3-billion-piece DNA profile, each individual's DNA has about 3 million points of difference from that typical profile. In other words, "the copy of genes you got from your mother differs from the

copy you got from your father by about 3 million changes," Pennacchio says. In addition, "very recent data suggest that you'll have about 50 [genetic] changes that neither your mom nor your dad had, due to recent mutations," he says.

These 50 changes are essentially copying errors that occur by chance as we grow "to have a hundred million cells that evolved very quickly from two cells" — egg and sperm — at conception, explains James P. Evans, professor of genetics and medicine at the University of North Carolina, Chapel Hill.

Gene science and epidemiology have revealed that for many common diseases, such as high blood pressure and diabetes, about half of an individual's risk of developing the disease comes from genetics and the other half from the environment, says Pennacchio. "As a scientific community, we would like to learn what is the part that's genetic and, as the holy grail, be able to take a person's individual gene sequence" and understand "their sensitivity to drugs and their risk" for some diseases.

Science continues to advance toward those goals, but to some extent hype and hope have surged ahead of understanding, says Evans.

For example, DTC tests like those Collins tried out "have been tremendously overhyped," he says. That's because, while scientists have identified quite a few genes that are associated with a population-wide risk of various conditions, "we have no idea how to come up with the net risk" of an individual for anything except the rare diseases that are caused by single genes or mutations, such as cystic fibrosis.

In 2010, a House oversight panel held a hearing on DTC testing, and the FDA announced plans to set up a regulatory scheme for the tests, which it classifies as medical devices, since they are intended to diagnose individuals' risk of developing particular diseases. In May 2010, for example, San Diego-based Pathway Genomics and the pharmacy chain Walgreens announced plans to sell Pathway's genetic test kits at Walgreens stores, but the FDA quickly raised questions and the companies put their plans on hold.³

"It's little wonder that when we have a scientific advance the public gets impatient to see it applied to medicine" via high-tech magic bullets like gene therapy or risk prediction, Evans says. But given "the degree of scientific illiteracy on the part of the population," together with the "hopes for commercialization" on the part of businesses and researchers, "it's no surprise that expectations [for what the science can accomplish or, at least, accomplish quickly] often are unrealistic."

Another source of controversy is whether the genetics field will move faster or slower toward effective diagnostics and treatments if the government continues to grant some kinds of gene patents.

The American Civil Liberties Union is suing the U.S. Patent and Trademark Office and Salt Lake City-based Myriad Genetics Inc., to end Myriad's exclusive control over two genes implicated in breast and ovarian cancer and to stop the Patent Office from granting patents on isolated but unaltered genes. Late last year, the Department of Justice issued a brief opposing such patents.⁴

"If you want to look at your own genome and see if you have a mutation, you should be able to do that without paying a license fee to someone else," said Steven Salzberg, a professor of computer science and genetics at the University of Maryland, College Park.⁵

But denying patents for isolated, naturally occurring genes "would destroy the U.S. biotechnology sector," which depends on patent exclusivity for revenues, argued patent attorney Gene R. Quinn of Melbourne, Fla.⁶

As gene science advances, here are some of the questions being asked:

Are effective therapies derived from gene science on the horizon?

In the heady genome-exploration days of the 1990s, hopes ran high that far more effective medicines derived from gene science were just around

How to Create Your Family Health History

A family health history reveals diseases that run in your family and environmental influences — such as eating habits and activity levels — that your family shares. Knowing your family health history has always been an important part of medical prevention and diagnosis. But as genetic testing becomes more prevalent, family medical histories are key to linking genetic profiles to patterns of health and disease.

To assemble a family health history:

- Start by collecting medical history information for yourself, your parents and your siblings; then move on to grandparents, aunts, uncles and cousins if you can;
- Record your relatives' ages, names, genders and relationship to you; ethnicity and date and place of birth; any health conditions they've experienced and how old they were when the condition began;
- Include information about the environments family members lived in and their lifestyles, including occupation, place of residence, diet, smoking status, and whether a person was active or sedentary;
- Record the age and cause of death of deceased family members. Obituaries and death certificates may contain this information if living family members don't know it;
- Seek information if you're adopted; your adoptive parents may have been given some information about your biological parents' health. Laws in some states allow adoptees to request the medical records of biological parents. A medical history that includes information about your lifestyle and environment and that of your adoptive family can also help your doctor understand your risks for many diseases;
- Keep your history updated. Having full information can help a physician better diagnose problems for you and your family.

Source: American Society of Human Genetics, www.talkbealthistory.org/family/faq.shtml

the corner. Many experts predicted that gene therapy, as well as traditional drugs discovered as scientists unraveled the genetic code, would soon be on the market.

But many researchers now say that unexpected complexities in the science make the road to practical results much longer than once believed.

"Skepticism about the Human Genome Project is misplaced," says Anindya Dutta, a professor of biochemistry and molecular genetics at the University of Virginia. The project "has delivered an

amazing number of new things," utterly changing "the way scientists think about disease and how we do science."

To cite just one example, Dutta explains that scientists now mainly describe specific cancers by the exact sort of genetic damage — called a "molecular lesion" — that triggers them, rather than by the organs they're located in, such as the lungs or the stomach. "The molecular classification gives a much clearer view" of the possibilities for treatment, he says. For example, already diagnostic labs "can go straight to the

DNA and find exactly whose cancer can be effectively treated” by Herceptin, a drug that apparently slows out-of-control cell growth in some breast cancers.

So far, however, no actual gene therapy has proven safe and successful in humans, although researchers continue to pursue avenues they believe show promise.

At an American Heart Association meeting last November, researchers reported that in early trials a potential gene-therapy treatment for advanced heart failure appears to be safe and possibly effective. Patients in the trials underwent a cardiac catheterization procedure to receive a gene engineered to stimulate production of an enzyme that helps the heart pump more efficiently. Of nine patients who received the gene, seven showed some improvement in their condition, including improved heart function, and the treatment didn’t appear to create serious side effects.⁷

“We are encouraged by these initial findings,” said principal investigator Donna Mancini, a professor of medicine at Columbia University’s College of Physicians and Surgeons in New York City.⁸

Thanks to high-speed gene-sequencing technology developed through the Human Genome Project, finding the genes associated with a given disease is now relatively simple, says Gerard D. Schellenberg, a professor of pathology and laboratory medicine at the University of Pennsylvania. Essentially, he explains, researchers sequence the genomes of many people who have a disease and search for genetic variations they may have in common.

Once scientists know which gene variations are associated with a disease, they must also learn how those genes function normally in our cells — via so-called molecular “pathways” — when we’re healthy and what might go wrong with those pathways that create a disease state, Dutta says.

“This is doable, but much different” from sequencing genomes, says Schel-

lenberg. For one thing, in many cases, even when the genes associated with a disease are found, scientists have no idea what normal cell functions those genes relate to, he says. New technologies continue to make sequencing and analyzing genomes faster and faster, but “a lab will work for years and years” to figure out how a gene relates to cell function. For example, it’s been known since 1987 that the so-called APOE gene is strongly linked to Alzheimer’s disease, says Schellenberg. “But we still don’t know the normal function of that protein” in cells.

Progress in developing treatments from gene science has been agonizingly slow and is likely to remain so, James Le Fanu, a London-based general-practice physician, wrote in the *British Medical Journal*.

“Nearly 10 years have elapsed since the completion of the first draft of the Human Genome Project, with its ability to pinpoint the mutations responsible for more than 1,000 monogenic disorders,” Le Fanu wrote. Yet many of those single-gene disorders still aren’t even diagnosable through genetic profiles.⁹

Le Fanu even argued it is “conceivable that modern genetics might be a blind alley,” because evolution all but guarantees that no really lethal diseases caused by gene defects would ever be widespread. That’s because people with the defect would be less likely to survive and reproduce. “Natural selection has ensured that genetics is not a particularly important or modifiable factor in human disease.”¹⁰

Is selling genetic tests directly to consumers a good idea?

Direct-to-consumer sales of genetic tests were rare until November 2007, when three companies began offering them. Since then, tests have been easily available on the Internet, allowing people to send a DNA sample — usually saliva — to companies such as California-based 23andMe and Navigenics and, for a few hundred dollars, get back information

about their genetic ancestry and medical risks.¹¹

DTC vendors say the tests help curious people learn about themselves and that their analyses are based on the best current scientific understanding. Critics, however, contend the science of genetic testing isn’t far enough along to yield meaningful results.

“Customers empowered with this information have made lifestyle changes aimed at reducing their risks of developing disease and have provided information to their doctors to aid in diagnosis and treatment. These actions have improved and even saved lives,” 23andMe general counsel Ashley C. Gould told a House oversight committee last July.¹²

While saying she could not speak for the whole industry, Gould said her firm provides “extensive information to our customers so they understand that the data we provide can change as new scientific studies are completed.”¹³

Purchasers of DNA health-risk profiles are mainly well-off, technically savvy people, so it’s not clear how far one can generalize from their response to DTC testing, said David Kaufman, director of research and statistics at the Genetics & Public Policy Center, a research and survey group jointly sponsored by the Pew Charitable Trusts and Johns Hopkins University. Nevertheless, current customers’ self-reported responses to test results suggest testing’s potential in preventive health, he said.¹⁴

Asked whether they’d made health-related lifestyle changes after DTC tests informed them they had medical risks, 34 percent of people surveyed by the center said they were more careful about what they ate, 14 percent said they exercised more and 16 percent had changed their medications or dietary supplements. “We don’t give enough credit to people’s abilities to decide what’s useful to them,” said Kaufman.¹⁵

But Congress’ nonpartisan auditing and investigative arm, the Government Accountability Office (GAO), blasted

current DTC tests in a report last July. After buying tests from four websites, GAO analysts created biographical profiles of several “fictitious consumers” of various ages, weights and lifestyle descriptions and submitted them along with DNA samples taken from only one woman and one man. Although the DNA came from just two people, the companies sent back a wide and bewildering variety of risk profiles and recommendations, the GAO said.¹⁶

“Although there are numerous disclaimers indicating that the tests are not intended to diagnose disease, all 14 results predict that the fictitious consumers are at risk for developing” conditions ranging from osteoporosis to cancer, presumably based on lifestyle profiles, not DNA, said Gregory Kutz, GAO managing director for forensic audits and special investigations. “If the recommendations were truly based on genetic analysis,” then all the fictitious females “should have received the same recommendations because their DNA came from the same source. Instead, they received a variety of different recommendations, depending on their fictitious lifestyles.”¹⁷

“Test results can be unreliable and difficult to interpret, and they are often offered to people with little or no genetic counseling or support,” said Christopher Hood, of the Nuffield Council on Bioethics in London. “People should be aware that other than prompting obvious healthy lifestyle choices such as taking more exercise, eating a balanced diet and reducing alcohol

consumption, the tests are unlikely to inform them of any specific disease risks that can be significantly changed by their behavior,” said Hood, chairman of the council’s Working Group on bioethics and Gladstone professor of government at All Souls College, University of Oxford.¹⁸

“With only a few exceptions, what the genomics companies are doing right now is recreational genomics,” said David B. Goldstein, a professor of molecular genetics and microbiology at Duke University.¹⁹



Getty Images/Donald Bowers

Google co-founder Sergey Brin and his wife, Anne Wojcicki, attend a celebrity “spit” party in New York in 2008 hosted by 23andMe, co-founded by Wojcicki. It’s among several companies selling genetic-testing kits, which enable people to send a DNA sample — usually saliva — and receive information about their genetic ancestry and, the companies say, their medical risks. Critics say the tests can’t accurately predict health risks.

Having access to one’s own sequenced genome, once that becomes feasible and affordable for everyone, won’t add much to most people’s understanding of their health risks, says Barbara Bernhardt, a genetic counselor and clinical professor of medicine at the Hospital of the University of Pennsylvania. “You’re going to find every single difference in your genome from what may be considered normal. But you won’t have a clue about what that means,” nor will anyone, including scientists, she says.

“Even highly educated people misinterpret test results,” says Kaufman of the Genetics and Public Policy Center. For example, told that a DTC test found a hypothetical woman having a risk of diabetes that was lower than the general population’s risk, 7 percent of people, most of them fairly well-educated, erroneously concluded that the woman actually was at high risk of the disease.

“People were more likely to misinterpret a low-risk number” as predicting a high risk, Kaufman says. This might happen “because people are just looking for high-risk information,” he suggests.

Timothy Caulfield, a professor of law and public health at the University of Alberta, one of Canada’s largest research institutions, said that in one study, a whopping 78 percent of people who said they are interested in being tested also said they “would ask their physician for assistance with interpreting the data. Further, 61 percent of respondents felt that physicians have a professional obligation to help with this interpretive process,” he said.²⁰

However, “the data is of only marginal health benefit,” according to most analyses, meaning

that the costs and time used up in those physician visits would provide “little or no health benefit” to anyone, Caulfield said. Cash-strapped health-care systems can ill afford such luxuries, he said.²¹

In addition, hopes by some that genetic testing will eventually hold down costs by dissuading doctors and patients from using medical treatments that gene tests show won’t work for them are probably overly optimistic, genetics counselor Bernhardt speculates.

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Gene Links to Prevalent Diseases Prove Elusive

When it comes to using genetics to unravel disease, different illnesses present different challenges.

“We now understand simple genetic disorders pretty well,” says Len A. Pennacchio, a geneticist at the Lawrence Berkeley National Laboratory, in California. For example, in the not-too-distant future, when a child with an apparent single-gene disease, such as cystic fibrosis, is born to parents who don’t show symptoms, it will be possible to sequence the child’s and parents’ genomes “to find out whether the disease has been inherited or is *de novo*” — freshly appearing in the child because of some new mutation, says Pennacchio.

Scientists also have unlocked more details about cancer than many other diseases, Pennacchio says. “Cancer is all about the DNA,” with environmental events such as exposure to the sun’s ultraviolet radiation triggering mutations that turn healthy cells malignant, he says.

Further, in cancer, only a localized group of cells — such as a tumor — goes awry, explains Pennacchio. New technology allows doctors to examine a patient’s typical DNA next to a tumor’s DNA to find the exact genetic differences that have presumably turned the ordinary tissues into cancer, he says.

Nevertheless, such analysis works only for early-stage cancers, explains Anindya Dutta, a professor of biochemistry and molecular genetics at the University of Virginia. One characteristic of cancer is a “unique ability to change its repertoire” through quick, multiple gene mutations. Late-stage cancers develop rather chaotically, so a cancer that begins with the same genetic profile in two people may develop into two quite different cancers in the late stages. This accounts for the extreme difficulty of developing effective treatments for late-stage cancer, Dutta says. As multiple mutations occur, about 1 percent of the cancer cells in each new generation will have a makeup that allows them to survive whatever defenses the body and medicine mount against them.

All widespread diseases besides cancer apparently have an even more complex relationship to genes.

For Alzheimer’s, for example, “there are some rare [gene] mutations that flat-out cause the disease,” and these have been found in families with a strong history of the illness, says Gerard D. Schellenberg, a professor of pathology and laboratory medicine at the University of Pennsylvania. Since these cases are essentially single-gene conditions, they have been relatively easy to track down by studying the genomes of families in which early-onset Alzheimer’s is common, he says. No more rare Alzheimer’s-triggering genes are likely to be found, Schellenberg adds. We “don’t see any families with generation after generation getting [Alzheimer’s] at an early age that we can’t explain” through mutations that have already been identified, he says.

But most people who develop Alzheimer’s will get the disease through a more complex route, with multiple genes helping to raise the risk of developing the disease.

To find out what those genes are, scientists scan the genomes of a large number of people who have the condition and a large number of people who don’t. They’re on the lookout for

gene variations — not mutations, but simply alternate forms of genes, called “alleles” — that occur in both the sick and healthy populations but “a little bit more often” in people who have the disease, Schellenberg explains.

With about 10,000 Alzheimer’s patients’ genes sequenced, “we’re up to about seven [additional] genes related to late-onset” Alzheimer’s, says Schellenberg. “These are pretty much small-effect genes,” and “when we get the next 10,000” people into gene-sequencing studies, “I’m sure we’ll find more.”

Like Alzheimer’s, other common conditions, such as high cholesterol and high blood pressure, are related to multiple genes, each contributing only a small amount to an individual’s risk of developing the condition. Scientists differ sharply on how useful these findings are for tailoring preventive-health strategies for patients or eventually developing gene therapies.

Currently, about 20 different genes have been shown to relate to heart-disease risk. Daniel J. Rader, scientific director of translational/clinical research at the University of Pennsylvania’s Institute for Translational Medicine and Therapeutics, says he has argued that the genes should be used clinically to determine whether people should take a blood-fat-lowering drug based on their genetic profile, even if they don’t have extremely high cholesterol.

Within the next few years, the medical field should arrive at the “point of saying to a 40-year-old male,” based on gene tests, family history and individual risk factors like smoking, that “for the average person, it’s a 50 percent risk” of heart disease over the next 40 years, “but for you it’s more like 80 percent,” and “if you take these steps, we can reduce it to 20 percent,” Rader says.

But others say that’s too optimistic — that the so-called genome-wide association studies intended to turn up common gene variations related to disease most likely are based on a false premise.

“After doing comprehensive studies for common diseases, we can explain only a few percent of the genetic component of most of these traits,” said David B. Goldstein, a professor of molecular genetics and microbiology at Duke University. “For schizophrenia and bipolar disorder, we get almost nothing; for type 2 diabetes, 20 variants, but they explain only 2 to 3 percent of familial clustering, and so on.”¹

The problem, Goldstein believes, is that evolution has been much more successful than many have believed at killing off people who carry disease-causing gene variations before they can reproduce. Thus, evolution has stopped most disease-causing alleles from ever becoming common. And most cases of so-called “common” diseases are probably caused instead by rare patterns of genetic variation that occur in only a few people, he speculates.²

— Marcia Clemmitt

¹ Quoted in Nicholas Wade, “Scientist at Work: David B. Goldstein,” *The New York Times*, Sept. 15, 2008, www.nytimes.com/2008/09/16/science/16prof.html.

² *Ibid.*

Continued from p. 55

Diseases once thought to be single conditions are now known to have quite different genetic origins in different individuals. As a result, scientists already know that people with certain genetic profiles simply won't benefit from some therapies. And such findings will certainly proliferate, Bernhardt says. But even if testing definitively demonstrates that a patient won't benefit from a given therapy, physicians will most likely prescribe it anyway, since "no one will do nothing" for a sick patient, she says.

Should the government award patents for "naturally occurring" genes?

An organism's genome is its complete set of DNA — two complementary strands of repeating chemical units called nucleotides, or bases, bound together like a spiral ladder and found in every cell of the body. A gene is any section of DNA that is inheritable as a unit from one's parents and contains the code for creating either a protein or some other molecule that performs a function in one's cells.

Scientists can manipulate genes by changing their nucleotide sequences, and early gene-science patents generally were awarded to such "human-engineered" genes or to techniques for gene manipulation. Such altered genes or lab processes are clearly inventions, and few argue that similar biotechnology industry products should not be patentable.

The U.S. Patent Office, however, also grants patents on naturally occurring genes that patent seekers have not altered except by isolating — removing — them from the whole length of the genome.

The American Civil Liberties Union (ACLU) and other groups are suing the Patent Office and Salt Lake City-based Myriad Genetics Inc. to end Myriad's exclusive control over two genes implicated in breast and ovarian cancer, BRCA1 and BRCA2, and to block similar patents in the future.²²

The U.S. Department of Justice (DOJ) recently sided for the first time with patent opponents and against the Patent Office, asserting in a brief that a district court has "correctly held . . . that genomic DNA that has merely been isolated from the human body, without further alteration or manipulation, is not patent-eligible." That's true, even though "many other genetic materials . . . and genetically modified crops should be eligible for patents," DOJ said.²³

Proponents of the patents claim that "isolated genomic DNA has practical uses that native DNA does not" and that patents provide "an incentive for companies to identify, describe and develop those uses into commercial applications that promote the public welfare."

But this argument "rests on several erroneous premises," the DOJ charged. "While isolated genomic DNA may have more potential applications than human genes in their natural context" — i.e., when they are attached to the whole genome — "the same is equally true of mined coal, separated cotton fibers . . . and other products of nature whose industrial value to mankind . . . arises when they are extracted from their naturally occurring environments."²⁴

"Patent law has long held that products of nature and laws of nature are not patentable subject matter," said the ACLU. The Patent Office "is failing to abide by this precedent when it grants patents on human genes." Furthermore, gene patenting is a civil liberties issue because the patents "undermine the free exchange of information and scientific freedom," ACLU said.²⁵

Patents can harm patients' access to genetic testing, according to the University of Alberta's Caulfield, Richard Gold, a professor of law at Montreal's McGill University, and Peter N. Ray, a professor of molecular and medical genetics at the University of Toronto. "Since all genetic tests require the reproduction of the patient's target gene," patent holders can make it hard

for some patients to get gene tests by keeping prices high or requiring all work to be done at their own labs, they said.²⁶

"About 20 percent of the human genome is under patent," said Evans at the University of North Carolina. "For genes such as those related to cystic fibrosis and Huntington's disease, which are not patented, a thriving marketplace exists where dozens of laboratories — both private and public — vie to out-compete one another on the basis of innovation, quality and service. However, for those genes controlled by patent-enabled exclusivity" physicians generally must use only one source for the genetic work, and there's no market competition to hold down price or drive higher quality or innovation, Evans said.

Many in the biotech industry say that denying the patents will cause "economic catastrophe," Evans acknowledges. But he says that only "a few companies" who derive their profits mainly from "eliminating competition" would suffer. Any genetic discovery virtually always has a host of other gene products and processes that would remain patentable, and businesses can derive healthy profits from those, he contends.²⁷

"Although a patent or exclusive license may at times stimulate its holder to develop a genetic test," there appear to be "no cases in which possession of exclusive rights was necessary for the development of a particular genetic test, including . . . tests for both common and rare genetic diseases," an expert panel reported to the U.S. Department of Health and Human Services last April. "Furthermore, exclusive rights do not result in faster test development," said the group, which included scientists, business people, lawyers and federal officials.²⁸

For example, some patients covered by Medicaid — a federal-state program for the poor — have been unable to get certain tests because the

patent-holding entity wouldn't accept their state's Medicaid payment, said the group. Exclusive licensing also prevents patients from getting a second opinion on test results.²⁹

Researchers seem divided about whether patents slow their work. In a Canadian study based on interviews with 20 gene scientists, nine said that patents' effect was neutral, seven said it affected their work negatively and four said it affected it positively.³⁰

Biotechnology companies argue strongly for allowing patenting of unaltered genes to continue, however.

"In an astonishing and irresponsible policy shift that directly contradicts the long-standing policy of the United States federal government and a variety of agencies, the Department of Justice is promoting the dialing back of what is considered patentable subject matter and is urging the Federal Circuit to rule that 'isolated but otherwise unaltered genomic DNA is not patent-eligible subject matter,'" said patent attorney Quinn. The move is part of the Obama administration's "anti-business policies" that are "costing Americans jobs," he charged.³¹

DOJ's argument that isolated genes have not been sufficiently altered to warrant patenting because "in nature there is no such thing as an isolated segment of DNA" is clearly invalid, said Quinn. "Only through human intervention is the segment of DNA capable of being extracted," and this fact makes the isolated gene not a product of nature alone but of human activity as well, which is clearly patentable, he said.³²

The Justice Department's position "ignores and trivializes the nature of what it takes to isolate human DNA that encode particular genes," said Kevin E. Noonan, a Chicago biotechnology patent lawyer. In fact, laboratories that isolate a gene perform "a chemical change on the molecule that is profound" — breaking its molecular bonds with the rest of the genome. This clearly makes an isolated gene patentable, he said.³³ ■

BACKGROUND

Maps of the Territory

Efforts to decipher the genomes of humans, animals and plants, including microorganisms, officially began in October 1990, when the federally funded Human Genome Project opened its doors.³⁴

The \$3 billion international effort to map the approximately 3 billion nucleotide molecules in a typical human genome completed its preliminary analysis of a full genome in February 2001, some five years ahead of schedule. For privacy's sake, this "reference" genome did not come from one individual but was assembled using DNA from several volunteers.

The initial mapping only scratched the surface of genetic understanding, however, and work continues on many fronts today. At the most fundamental level, scientists have learned that the biology of inheritance and the relationship between genes and disease are many times more complex than most imagined 20 years ago.

Notably, efforts began in the early 2000s to study the genetic profiles of many people in order to discover the most common patterns of genetic variation among individuals and, ultimately, learn which variations are associated with which diseases. In a line of research known as genome-wide association studies, scientists scan genomes in search of variations that appear more frequently in people with personal and family histories of certain medical conditions.

Most recently, scientists have begun to delve into areas of the genome formerly considered "dark" regions with no actual function in cells. They increasingly find that these regions likely play important roles in our bodies. (See sidebar, p. 62.)

Much new understanding has resulted, but perhaps the most important find-

ing is that virtually all diseases — even prevalent ones such as high blood pressure — are in essence multiple diseases, with different genetic profiles in different people, says Sharon F. Terry, president of the Washington-based Genetic Alliance, a coalition of more than 1,000 disease-specific advocacy groups. In effect, she explains, "Every disease is becoming a rare disease."

Goodbye, Silver Bullet

Traditionally, diseases were diagnosed based on symptoms. Among illnesses considered "rare" — affecting 200,000 or fewer Americans — many were known to be related to a gene variant or mutation, often inherited. Examples are the fatal childhood degenerative nerve disorder Tay-Sachs and cystic fibrosis. Meanwhile, conditions such as high blood pressure, which occur in large segments of the population, were considered "common" ailments.

In the 21st century, however, gene science has affected our picture of both categories of disease, says Terry, who became involved in patient advocacy in the 1990s after her two young children were diagnosed with pseudoxanthoma elasticum. PXE is a rare condition in which mineral deposits gradually accumulate throughout the body, destroying organs such as the eyes and heart. Gene science now provides diagnostic tests for many such rare diseases, although it has produced no therapies.

At the same time that more details have emerged in our knowledge of single-gene ailments, there has been a virtual revolution in scientific understanding of the many diseases formerly viewed as common. Genetics research repeatedly reveals that conditions once viewed as a single disease, such as breast cancer or type 2 diabetes, have very different genetic profiles in different people. Thus, virtually every disease will soon "be a

Continued on p. 60

Chronology

1940s-1970s

Scientists develop methods for studying the genetic code and unravel connections between genes and the operation of cells.

1941

American scientists George Beadle and Edward Tatum discover that each gene carries instructions to cells to produce one specific enzyme.

1959

German geneticist Friedrich Vogel coins the term “pharmacogenetics” for the study of how individuals’ genetic makeup relates to adverse drug reactions.

1977

English biochemist Frederick Sanger invents the first fast, accurate method of sequencing a genome.

1980s-1990s

Gene science burgeons.

1980

Supreme Court, in *Diamond v. Chakrabarty*, approves the principle of patenting genetically engineered life forms.

1988

Federal government begins planning the Human Genome Project to produce a full description of a human’s DNA sequence.

1990

Human Genome Project begins.

1994

American physician Ruth Decker develops a screening test for a rare form of thyroid cancer linked to a single gene mutation.

1998

Food and Drug Administration (FDA) approves Herceptin, a drug that lowers cancer recurrence and mortality for the 20 to 30 percent of breast cancer patients who have a particular genetic profile. . . . Clinton administration calls for legislation to bar employers from discriminating in hiring and promotion based on genetic makeup.

2000s

Human genome is sequenced and more genes linked to disease risk are found, but hopes fade for quick development of gene-based treatments.

2001

Faced with an Equal Employment Opportunity Commission lawsuit, Burlington Northern Santa Fe Railroad stops genetic testing of employees who file disability claims for carpal tunnel syndrome; the company had sought evidence that a gene abnormality caused the symptoms.

2002

University, nonprofit, government and corporate labs join in the International HapMap Project to discover the most common patterns of variation among individuals’ gene sequences.

2003

First detailed sequencing of the human genome published, at a cost of \$3 billion. . . . Scientists identify the rare gene variation that causes the devastating premature-aging disorder progeria.

2006

National Institutes of Health and some private companies open the Genetic Association Information

Network to use new rapid technologies and new maps of the human genome to compare the gene profiles of healthy people to those of people with diseases such as heart disease, Alzheimer’s, diabetes, osteoarthritis and stroke.

2007

FDA relabels the blood-thinning drug Warfarin, recommending that dosages be adjusted based on patients’ gene profiles.

2008

Genetic Information Non-Discrimination Act outlaws discrimination based on genetic information. . . . FDA recommends that patients undergo genetic testing before being prescribed the HIV drug Abacavir to prevent a potentially fatal allergic reaction. . . . Massachusetts General Hospital announces it will genotype every cancer patient.

2010

Government Accountability Office concludes that direct-to-consumer (DTC) genetic testing doesn’t provide reliable information about health risks. . . . After public outcry, California legislature kills a bill to exempt direct-to-consumer gene testing companies from regulatory oversight. . . . Swiss scientists find gene variant that predicts adverse reactions to hepatitis C treatment. . . . Cleveland Clinic researchers find that family medical histories predict cancer risk better than current DTC genetic-screening tests.

2011

Drug manufacturer Pfizer plans to submit a proposed new cancer drug to FDA for approval at the same time it submits a gene-diagnostic test to identify patients more likely to benefit from the drug.

DNA Databases Offer Both Promise and Peril

"I don't think my kids' DNA should be out there. If it is, it should be mine and their mother's decision."

Will research databases containing the DNA of hundreds of thousands of people compromise an individual's privacy?

That question dogs scientists' attempts to learn how genes raise the risk of prevalent diseases such as adult-onset diabetes. Another issue is whether genetic tests for disease risk and drug response will ever yield the clear-cut answers that could improve medical practice and health.

If scientists are to figure out which genes raise the risk of diseases, the medical histories of a very large number of people must be linked to their genomes, says Gerard D. Schellenberg, a professor of pathology and laboratory medicine at the University of Pennsylvania.

For example, researchers on blood cholesterol levels "have 100,000 people in their studies," but for Alzheimer's disease — Schellenberg's research area — "we're just creeping over 10,000" patients in the genome databases. That sample size "is small" for genetic research "so we can only detect genes that have a fairly big influence" on the disease, he says. As databases grow, "we'll discover more" risk factors, though ones with less influence.

But storage of health information for research makes some people highly uncomfortable. The Texas State Department of Health found that out in 2009, when it faced a lawsuit over its storing and distribution of blood droplets it had collected from newborns for years as part of a disease-screening program.¹

For years, Texas discarded the five blood drops it collected on a card from each infant shortly after a lab had screened them for genetic signs of diseases including cystic fibrosis. In 2002, however, without informing parents, the department began

storing the droplets, ostensibly for use in medical research. In addition, the state also sent 800 anonymous blood cards for inclusion in a national forensic DNA database project set up by the Armed Forces DNA Identification Laboratory. When parents and civil-liberties groups found out that the blood was being saved and forwarded to outside groups, they raised alarms.

"I don't think my kids' DNA should be out there, and if it is it should be mine and their mother's decision," said Michael Neff, whose two young daughters had samples in the bank.²

In late 2009, the state settled a lawsuit filed by the Austin-based grassroots group Texas Civil Rights Project, agreeing to destroy all past samples. A new state law that covers screening from mid-2009 onward allows parents to request that their children's samples not be stored.

That Texas officials began storing and forwarding samples without notifying the public "[raises] the specter that their motives aren't pure," said Texas Civil Rights Project attorney Jim Harrington.³

In surveys, people seem more interested in being informed about how their biological samples will be used than in preventing their use, says David Kaufman, director of research and statistics at the Washington-based Genetics & Public Policy Center, a joint project of the Pew Charitable Trusts and Johns Hopkins University. "People want as much transparency as scientists can give" about how their genetic data or physical samples will be handled and used, says Kaufman. If that's done, "then the large majority across demographic groups say they would support and maybe even participate in" genetic databases. "I think people actually are excited about it."

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rare disease," a circumstance that's both daunting and encouraging and will greatly alter medicine, Terry says.

For example, the aggressive brain tumor called glioblastoma is now known to have four different genetic profiles, says the University of Virginia's Dutta. In other words, "there are four major pathways that can keep the tumors from developing. We've gotten rid of the frightening idea that every individual's cancer is different." That fear haunted early genetic researchers who initially discovered that different glioblastoma patients had different gene profiles. Such a finding might have ended all hope of developing treatments, but scientists can now concen-

trate on studying the four varieties. "We wouldn't know that without sequencing the whole genome," says Dutta.

But treatments have come slowly. Gina Kolata, a longtime science reporter for *The New York Times*, recalled recently that a quarter-century ago, during a job interview at a news magazine, she was asked what the most important medical news of the next year would be. Kolata replied "gene therapy" — using actual genetic material to "repair" a person's own disease-inducing DNA.³⁵

The prediction was, to put it mildly, off the mark. Twenty-five years on, "I am still waiting for that to happen," Kolata said.

She was far from alone in her expectation. While scientists still actively pursue gene therapy today, especially in animal studies, the FDA has not yet approved any human gene-therapy product, and "little progress has been made since the first . . . clinical trial began in 1990," says the government's Human Genome Project information website.³⁶

As Dutta puts it, "If you're hoping to cash in on the stock market in five years" with a gene-based treatment, "things are bad. But if you are a scientist looking to find out how the body works, things are good."

Several high-profile patient deaths contributed to slowing gene-therapy research.

The Texas newborn screening debacle is “an excellent example of what the lack of transparency does,” says Kaufman. “Now that database has been completely destroyed,” an unfortunate outcome for researchers that he says may not have been necessary if the state had informed the public from the outset.

In the genome age, having large databases of DNA samples linked to people’s medical histories is a research holy grail.

For that reason, says Marcy Darnovsky, associate executive director of the Berkeley-based Center for Genetics and Society, people should be aware that whenever they are encouraged to give a DNA sample, their medical history and DNA — presumably stripped of personally identifiable information — may end up in such a database.⁴

For example, people who submit their DNA to the Mountain View, Calif.-based DTC “personal genomics” company 23andMe “cannot opt out of having their information anonymously shared with researchers,” said Darnovsky. The company states this in its documents, but many miss the fact. The line was “buried” in a *New York Times* account of a celebrity DNA-collection party the company hosted, she said. The company’s real, though unadvertised, “business plan isn’t selling . . . DNA tests but compiling databases full of genetic information that it can sell to medical researchers,” Darnovsky said.

Meanwhile, questions persist about when and whether genetic profiles will provide the kind of clear answers about health risk that doctors and patients crave.

The cancer drug Herceptin, for example, has been found to prevent cancer recurrence and reduce mortality risk for patients whose tumors have extra copies of the protein HER2.

However, the genetic tests to determine whether a tumor fits the profile “can be surprisingly unreliable,” *The New York Times* reported last year.⁵

For example, a “mosaic-pattern” tumor — in which one part tests positive for HER2 and the rest negative — isn’t uncommon and leaves doctors in a quandary. Furthermore, the HER2 test produces about 20 percent false-positive results — finding a tumor susceptible to the drug when it is not — and 5 to 10 percent false negatives.

A wrong answer on Herceptin has health and financial consequences. A year’s supply costs \$42,000 wholesale, and the drug has side effects, including a small chance of severe, potentially fatal, heart damage. That, said Antonio Wolff, a breast cancer specialist at Johns Hopkins, makes it a “toxic and expensive placebo” if a patient who would not be helped takes it.⁶

— Marcia Clemmitt

¹ For background, see Martin Bartlett, “State Agrees to Destroy Controversial Infant Blood Samples,” KVUE TV, Dec. 22, 2009, www.kvue.com/news/State-agrees-to-destroy-infant-blood-samples-79934742.html, and “Topic Update: DNA Databanks,” *GeneWatch*, March/April 2010, www.councilforresponsiblegenetics.org/GeneWatch/GeneWatchPage.aspx?pageId=258.

² Quoted in Bartlett, *op. cit.*

³ Quoted in *ibid.*

⁴ Marcy Darnovsky, “The Spitterati and Trickle-down Genomics,” *Biopolitical Times blog*, Center for Genetics and Society, Sept. 17, 2008, www.biopoliticaltimes.org.

⁵ Gina Kolata, “Cancer Fight: Unclear Tests for New Drug,” *The New York Times*, April 19, 2010, p. A1.

⁶ Quoted in *ibid.*

In 1999, Jesse Gelsinger, an 18-year-old from Arizona who had a mild form of a liver disease caused by a genetic mutation, died while participating in a gene-therapy trial. Gelsinger was enrolled in the trial despite some medical characteristics that probably should have made him ineligible, such as the fact that his disease symptoms were mild and under control. He apparently suffered a massive immune reaction to the virus that was used to carry an altered gene into his cells.³⁷

Following an outcry, the FDA temporarily halted gene-therapy trials at the University of Pennsylvania, where Gelsinger’s trial took place. The FDA also investigated trials at a handful of

other institutions but took no broader action after the youth’s death.³⁸

In January 2003, however, the agency temporarily halted all gene-therapy trials after two children in a French experiment to treat an immune-system disorder developed a leukemia-like condition.³⁹

Even as the pace of human trials slowed, troubles continued.

In 2007, a trial for rheumatoid-arthritis therapy was temporarily shut down after a 36-year-old Springfield, Ill., woman, Jolee Mohr, developed a severe infection, followed by organ failure and death, soon after being injected with genetic material. Analysts later determined that Mohr died because of a se-

verely compromised immune system, not from the injection.

Because Mohr’s arthritis was controlled by existing drugs, her death raised questions about the advisability of gene-therapy experimentation except in cases of severe, life-threatening diseases for which patients’ risks of death or disability is even higher than those from the clinical trials themselves.⁴⁰

Today, government scientists have identified several factors that make effective gene therapy difficult:

- Human cells continually divide, making it hard to ensure that injected foreign genetic material will remain intact and active; thus, even successful treatments might be temporary;

Genome ‘Darker,’ More Tangled Than Once Imagined

“The interesting thing is how much of the genome had been overlooked as junk.”

Judging by headlines in recent years, one might conclude that scientists have an excellent handle on how genes influence just about every one of our traits, choices and behaviors.

“U.S. scientists have a message for liberal voters: Blame it on your genes,” says a recent article describing research published in a political-science journal. It traces left-of-center thinking to a specific gene variation combined with “the environmental condition of having many friends in adolescence.”¹

“Genes May Time Loss of Virginity” trumpets a 2009 headline reporting a finding “that genes explain a third of the differences in participants’ age at first intercourse.”²

For many scientists, though, the main takeaway of recent research is not the possibility that genes explain many human traits but the certainty that the genome and the process of inheritance are far more complex than just about anyone imagined.

“The interesting thing is how much of the genome had been overlooked as being junk,” or so-called “dark” DNA, says Anindya Dutta, a professor of biochemistry and molecular genetics at the University of Virginia. Dark DNA is DNA inherited from parents that doesn’t seem to do what “genes” are traditionally thought to do: carry instructions for making proteins or other molecules used by the cells, Dutta says. Over the past few years, many scientists have concluded that this dark DNA — long thought to be essentially dormant — actually performs vital functions, although many of those functions are yet unknown, Dutta says.

Unlike genes — the segments of the 3-billion-molecule-long genome that carries the instructions people inherit for building

proteins — dark DNA was little studied until recently. But that’s changing fast.

“My current interest is in the dark matter” that makes up about 98 percent of the genome, says Len A. Pennacchio, a geneticist at the Lawrence Berkeley National Laboratory, in California. It’s becoming apparent that various islands within “dark matter” DNA act as regulators of gene “expression” — determining when and where in our bodies different genes are turned on and off, he says.

The importance of gene expression becomes clear when one realizes that each of the body’s cells has the same DNA sequence, yet the body contains a very large variety of cells, such as heart cells and muscle cells. How does the identical DNA “blueprint” create so many kinds of cells? Different genes become active at different times and places in different tissues — a process called “gene expression,” says Pennacchio. Scientists increasingly understand that much of this “gene expression” is “regulated by pieces of DNA” in the “dark matter,” often DNA that’s far distant in the genome from the gene being regulated, he says.

Because of this potential regulatory function, a good chunk of genetic risk for some prevalent diseases may also lie in the dark DNA, says Pennacchio. For example, his lab recently found a chunk of hitherto unexplored DNA that is related to the development of coronary artery disease. It discovered that the DNA segment’s function seems to be to regulate the expression of a pair of genes that slow the rate at which cells divide. One possibility is that a version of the dark DNA allows the rate of cell division to speed up, which could lead the

- The immune system aggressively attacks foreign objects, including injected genetic material;

- Viruses used to carry genetic material into the cells can trigger immune-system reactions; and

- Many genes, not one, are behind most diseases, so single-gene therapies probably won’t work for the vast majority of illnesses.⁴¹

ations affect the liver’s production of enzymes that metabolize drugs, research has revealed that people with some genetic profiles break down drugs too quickly, causing side effects, or too slowly, weakening therapeutic value.⁴²

“We are gaining insight and will gain much more into how to use existing drugs more efficiently,” says the University of North Carolina’s Evans. “The poster child for pharmacogenomics is the HIV/AIDS drug Abacavir. It has now become standard practice to test for certain alleles” — alternative forms of a gene — before prescribing it, he says. “We are also seeing hints that there are other drugs for which genomics may be useful, such as tamoxifen [an anti-estrogen drug used for some forms of breast cancer] and Plavix [the brand name for the

blood-thinning drug clopidogrel].”

So far, however, scientists have only “limited knowledge of which genes are involved with each drug response,” and different genes may be involved for each of the thousands of pharmaceuticals now in existence, observes the federal genome website. Further, “since many genes,” not just one or two, likely influence response, “obtaining the big picture on the impact of gene variations is highly time-consuming and complicated.”⁴³

Pharmacogenomics also raises economic and ethical issues. For example, when only one or two drugs are available to treat a given condition, and they are found not to work in people with certain genetic profiles, those patients are still likely to demand treatment. Most

Genes and Drugs

As expected, pharmacogenomics — the study of how an individual’s genotype affects that person’s response to medications — is yielding some of the early health-care payoffs from gene science. For instance, since genetic vari-

body to produce an oversupply of cells in the arteries, clogging them and creating a predisposition to heart attacks.³

Other recent research focuses on a genome phenomenon that may be even more surprising: The environment can change gene expression, and some changes are passed on from generation to generation even though they don't involve actual changes in the DNA itself.

This surprising phenomenon involves what's called the "epigenome" — molecules that aren't strictly part of the DNA sequence but that surround DNA. For example, scientists have long known that clusters of atoms called methyl groups attach themselves to DNA and can play a role in regulating gene expression. Biologists previously believed that environmentally triggered changes to these epigenetic "switches" could not be passed on to future generations. Recently, however, it's been discovered that at least some environmentally triggered changes in epigenetic switches can be inherited.⁴

In a recent study, researchers at the University of New South Wales, in Australia, found that the offspring of male rats who'd grown obese and insulin-resistant after being fed a high-fat diet developed insulin resistance themselves, even though they'd never been fed high-calorie foods. In other words, the rats inherited a trait that their fathers had gained through environmental exposure.⁵

In another experiment, fruit flies exposed to a certain drug developed unusual growths on their eyes that persisted through 13 generations, even though their DNA sequences had not changed.⁶

Other surprising findings:

- After sequencing the human genome, researchers realized that of all the body's cells, only 10 percent are human, while the rest belong to microorganisms that live on and within us, says Dutta.
- About a third of the human genome, by weight, consists of "transposons" — pieces of DNA that can move to different places along the DNA sequence. Once considered "junk" DNA, they're now thought to be among the many factors that regulate gene expression, perhaps by damping genes but not turning them off entirely, thus potentially influencing the development of some diseases.⁷

— Marcia Clemmitt

¹ Braden Sims, "Conservative Scientists: Liberal Gene Discovered," *Metro Online newspaper*, Oct. 28, 2010.

² Ewen Callaway, "Genes May Time Loss of Virginitiy," *New Scientist online*, March 31, 2009, www.newscientist.com/article/dn16876-genes-may-time-loss-of-virginity.html.

³ Dan Krotz, "From Uncharted Region of Human Genome, Clues Emerge About the Origins of Coronary Artery Disease," press release, Lawrence Berkeley Laboratory, Feb. 21, 2010, <http://newscenter.lbl.gov>.

⁴ For background, see "Epigenetic Therapy," *Ghost in Your Genes*, Nova, PBS, www.pbs.org.

⁵ Sharon Begley, "Sins of the Grandfathers," *Newsweek*, Nov. 8, 2010, p. 48.

⁶ John Cloud, "Why Your DNA Isn't Your Destiny," *Time online/CNN*, Jan. 6, 2010, www.time.com.

⁷ "The Genome's Traveling Salesmen," press release, Johns Hopkins University, Feb. 14, 2009, www.hopkinsmedicine.org/news/media/releases/2009.

physicians are reluctant to refuse and may also argue — based on the fact that science is always a bit uncertain — that there is at least a tiny chance the treatments may work. As a result, gene science presents patients, physicians and insurers faced with paying for treatments with new dilemmas.

In the past, drug companies have relied on so-called "blockbuster drugs" — designed to treat conditions presumably shared by tens of millions of people — to generate the revenues needed to pursue pricey research and still earn profits. It's not clear how drug development will proceed in an age of "personalized medicine," when scientists discover that many, if not all, drugs, old and new, actually work well for much smaller groups of people.⁴⁴

Despite the remaining hurdles, research to understand conditions such as high cholesterol is "dramatically different" than it was several years ago, and in ways that will eventually facilitate both disease prevention and drug discovery, says Daniel J. Rader, scientific director of translational/clinical research at the University of Pennsylvania's Institute for Translational Medicine and Therapeutics in Philadelphia.

Thanks to superfast gene-sequencing methods developed through the Human Genome Project, scientists can now perform "unbiased" scans of many individuals' genomes to reveal which gene variations occur more often in people with a given medical condition than in the general population. In the past, when sequencing was slower and more expen-

sive, researchers could afford to look only for genes that they'd already hypothesized were involved in a disease, Rader explains.

The new and improved scans have enabled scientists to quickly add more than 60 genes to a longstanding list of 30 genes known to be involved in cholesterol metabolism. But for at least half the new group, scientists don't understand their normal function in cells. Nevertheless, the genes provide new avenues for researching what proteins or other gene products in the cells could be targets for new drugs, Rader says.

Genetic Law

Hopes and fears about gene science have led some lawmakers

Law Protects Against Misuse of Genetic Information

As scientists discover that many illnesses are inherited, lawmakers and the public have worried about the risk of genetic discrimination. Will insurance companies raise a person's health-insurance premiums if they discover that cancer runs in the family? Would an employer fire a worker with a family history of Alzheimer's?

Such concerns led to passage of the Genetic Information Nondiscrimination Act, signed by President George W. Bush on May 21, 2008. The law outlaws discrimination in health insurance and employment based on genetic tests or family medical history.

Among its provisions:

- Health insurers cannot require people to provide genetic information about themselves or family members for the purpose of eligibility, coverage or price-setting decisions;
- Health insurers can require genetic testing if an enrollee submits a claim for a treatment for which gene testing is needed to determine effectiveness or risk of side effects;
- Health insurers may request but not require enrollees to take genetic tests for use in medical research in which the insurer participates along with a research organization;
- Employers may not use genetic information in decisions about hiring, firing, promotion, pay or conditions of employment;
- Employers and labor unions may not use genetic information to make decisions about admittance to training programs;
- Unions may not expel or discriminate against people based on genetic information;
- Employers, employment agencies and unions may have access to an individual's genetic information only if it is publicly available or an employee authorizes its release.

The law does not:

- Protect against genetic discrimination involving life, disability, or long-term-care insurance;
- Override state genetic-discrimination laws that have stricter consumer protections than the federal law;
- Apply to the U.S. military.

Source: "What Does GINA Mean?," Coalition for Genetic Fairness, www.geneticfairness.org.

to propose several kinds of legislation over the past several years, and in 2008 they enacted a major federal genetic antidiscrimination law.

Two years earlier, then-Sen. Barack Obama, D-Ill., introduced the Genomics and Personalized Medicine Act to build

a federal infrastructure to bolster and oversee genetic medicine. Among other provisions, the legislation would create a national research biobank to collect human DNA samples along with related medical information and also authorize a federal crackdown on mis-

leading marketing of DTC tests. Introduced in some form in each of the past five years, the bill has never emerged from committee.⁴⁵

In 2007, Reps. Xavier Becerra, D-Calif., and Dave Weldon, R-Fla., introduced legislation to ban patents on genes, either naturally occurring or modified. The measure goes much further than the 2010 Department of Justice recommendation to ban patents on naturally occurring genes, but Congress has never acted on it. Granting gene patents prevents "critical research from advancing because scientists are wary of trespassing patent laws," said Weldon.⁴⁶

In 2008, Congress passed a law that had been on its agenda for nearly 15 years: the Genetic Information Nondiscrimination Act (GINA), aimed at keeping individually identifiable genetic information private and preventing discrimination based on genetics or family health history. In the mid-1990s concerns grew that employers and others might use genetic information about health risks as a basis for discrimination in hiring, insurance coverage and the like.⁴⁷

Some Democratic lawmakers and civil rights advocates such as the ACLU pressed for a law to protect the privacy of genetic information. But a Republican-led Congress resisted, in part because many large employers and the pharmaceutical industry opposed it. Drug companies, for example, worried that shielding genetic information too tightly would make it harder for them to figure out what medications would be profitable to develop. When Democrats gained the majority in Congress in 2006, however, the legislation began to move. It was signed into law by President George W. Bush on May 21, 2008.

Fears that the law will harm businesses by keeping them from doing population-level research on genetic information are understandable but unfounded, said Rep. Louise Slaughter, D-NY, a longtime backer of the legislation. The law denies access only to

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At Issue:

Do genetics tests help consumers improve their health?



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TESTIMONY BEFORE HOUSE ENERGY AND COMMERCE
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JULY 22, 2010

Since the completion of the Human Genome Project, scientists, physicians, policy makers and consumers have eagerly anticipated the era of “personalized medicine,” which means providing targeted preventive care and therapeutic treatment based on an individual’s genetic makeup.

Today, billions of dollars in research are being dedicated to building on our current knowledge of the human genome. Almost daily, new and exciting discoveries about the relationships between genetics and our health are transforming traditional medicine.

Empowering consumers with information about their genes holds tremendous promise to promote health and improve lives. We at Pathway can attest to the positive value that genetic information has provided to the lives of our customers. Moreover, Dr. Francis Collins, MD, Ph.D., the current director of the National Institutes of Health, cited several instances in his book *The Language of Life* where individuals have learned from genetic reports and proactively made changes to prevent or manage disease. As a physician, Dr. Collins knew he needed to incorporate a healthy diet and regular exercise in his life, and his genetic testing finally motivated him to make these changes.

Some have argued that consumers should not be provided with information about their genes, based on a fear that the information would not be used appropriately, or that genetic testing might create unnecessary anxiety amongst patients who feel destined to get certain diseases based on their genes. However, we believe that consumers are capable of understanding . . . that genetics are only one piece of the puzzle of living a healthy life.

Moreover, in 2009, Boston University School of Medicine’s Risk Evaluation and Education for Alzheimer’s Disease study found that asymptomatic first-degree relatives of Alzheimer’s patients who received genetic testing results regarding a possible propensity for Alzheimer’s disease did not have a change in the levels of anxiety, depression or overall general distress. While this study certainly highlights the need for responsible delivery of this information, it also indicates that patients are able to process genetic information effectively and use it to make better health decisions, even with respect to diseases like Alzheimer’s.

Companies like Pathway are allowing individuals and their physicians to accurately determine their personal genetic makeup. As new genetic findings are made and validated, Pathway updates individuals about these discoveries, and in consultation with their physician individuals can use this information to improve the quality of their health care.



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truly participatory, individualized medicine is a worthy goal and one we should strive for. People should have access to the information contained in their own genome. But it is also critical that they be assured that claims made by the purveyors of such testing comport with reality.

Unfortunately, this is not always the case, at present. The most egregious problem is the distinct gap between claims made by the providers of such services and the value of the information actually imparted.

We hear claims that scanning your genome for genetic variants provides a “road map to better health,” allows one to “take control of your health future” or that “knowledge is power” with regard to disease. These are the central advertising logos of the three most prominent players in the genomic DTC [direct-to-consumer] arena. Yet on each page of every report provided to patients by these companies, some variant of the following disclaimer is made: “Information provided is not intended as, nor does it provide, medical advice, treatment, diagnosis or treatment guidelines.”

The explicit health claims and the accompanying disclaimer (in tiny font) cannot both be true. Indeed they are not. The disclaimer is correct. Such information, by and large, utterly lacks medical significance. This would be true even if we understood how to interpret such tests, which we do not.

It is often submitted by boosters of such technology that mere knowledge of one’s risks will be of benefit to an individual. Yet, little evidence suggests that this is the case. Statistics about risk are tricky.

I know, to a first approximation, what you, the reader of this document, will likely die of: cardiovascular disease or cancer. These maladies are not called “common diseases” for nothing. One is at considerable risk for them regardless of whether one happens to be at a relatively increased or decreased risk when compared with the average individual in the population. Thus, even for those at decreased relative risk, the chances are that they too will die of one of these common diseases. Thus, finding out that you’re at double or half the “average” risk of a common disease is simply not medically meaningful.

Some claim that knowledge of an increased risk will motivate people to live more healthy lifestyles. Yet there is no good data thus far that genetic information has any special qualities that will motivate individuals any more effectively than do our current admonitions.

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genetic information that can be linked to specific, named individuals. “I don’t object to” drug companies using genetic information for research, “but I saw no reason for them to know who this person was, where they lived or where they worked,” Slaughter said.⁴⁸

Protecting personal medical information is crucial, but, ironically, “our ignorance about the genome means we probably have much less to fear on genetic privacy than some would tell you,” the University of North Carolina’s Evans says. Even if one’s full genome were sequenced, published and analyzed based on all available research, “I still couldn’t tell much about you.” ■

CURRENT SITUATION

Genetic Testing

With actual treatments created by gene science likely many years away, scientists today are debating whether gene testing is helpful for the general public or even, in some cases, for physicians.

Many single-gene diseases, such as the rare Tay-Sachs and cystic fibrosis, can now be quickly and accurately diagnosed. Further, when a child’s genome is compared to those of the child’s parents, some such diseases can be characterized as either inherited or *de novo* — stemming from a mutation that’s occurred for the first time in the child rather than passed on. Uncovering such information is a huge benefit that “helps parents with reproductive planning,” says Evans. Nevertheless, treatments aren’t available for most single-cell diseases, “and a diagnosis for which there’s no treatment is basically only a consolation prize,” he says.

For more common health conditions,

such as heart disease, Alzheimer’s and type 2 diabetes, the picture is cloudier. For the vast majority of people with commonly occurring conditions, many genes appear to be associated with the diseases, and any one gene contributes only a small amount to the risk they face, says Evans. Further, scientists are largely in the dark about how the interactions among genes or environmental influences — which range from food to air quality to hormone exposures in the womb — affect disease development.

Thus, when scientists scan the genomes of a large number of people and find that a gene is “associated” with a disease, “you can say that the gene has an effect” in influencing the disease at the level of the whole population, but its actual predictive value for an individual is extremely limited today because too many complex and little-understood factors are involved, explains the Department of Energy’s Pennacchio.

That scientific uncertainty lurks behind current debates.

Over the past few years, Alameda, Calif.-based Celera Corp.* has sold doctors about 160,000 genetic tests intended to predict risk of coronary artery disease (CAD) based on whether the individual possess a variant form of the so-called KIF6 gene.⁴⁹ In the past, research has found a strong association between the gene and CAD.

Last November, however, a new study involving 57,000 people in several countries reported an opposite finding: that the gene variation “was not associated with the risk” of CAD.⁵⁰

“This study puts the nail in the coffin” of hopes to use the gene variation as a predictor of CAD, declared Thomas Quertermous, a professor of cardiovascular medicine at the Stanford University School of Medicine.⁵¹

Celera strongly disagrees, contending the 2010 study’s numerous biases

* Celera was founded in 1998 by biologist J. Craig Venter, a genome-sequencing pioneer. Venter stepped down as Celera president in 2002.

and problems cast doubt on its results. “We believe that the case-control study of coronary artery disease” published in November does not accurately replicate earlier “rigorous prospective and randomized controlled trial” research that found the KIF6-CAD connection to be strong, said Thomas White, the company’s chief scientific officer. Among the alleged problems: A large number of the study’s 83 international coauthors “are employed by a commercial firm that sells a competing genetic test” for coronary risk, said White.⁵²

Testing and the Public

Even more controversy surrounds genetic tests provided directly to the public.

In a 2010 study, for example, Charis Eng, director of the Cleveland Clinic’s Genomic Medicine Institute, reported that family medical histories turned up many more people at high risk for cancer than DTC tests.⁵³

For example, the family histories of nine people in Eng’s study revealed strong hereditary risk for colorectal cancer, and five of the nine actually turned out to have gene mutations linked to the disease. But a commercial test didn’t identify any of the nine as being at high risk, said Eng.⁵⁴

Also in 2010, San Diego-based Pathway Genomics and Walgreens pharmacies announced plans to sell Pathway’s genetic test kits, but FDA questions forced the companies to put their plans on hold. The FDA has jurisdiction over medical diagnostic tests that are developed in laboratories. But until the announcement FDA “had not asserted their enforcement authority over these tests,” noted a staff memorandum from the House Energy and Commerce Subcommittee on Oversight and Investigations.

Last May, however, the FDA told Pathway the agency had the authority to regulate how and where the tests are marketed because they fall under

the legal definition of “medical devices” intended to diagnose health conditions. Last summer, the FDA informed other DTC companies about its authority and began developing a regulatory strategy.⁵⁵

“Some companies are making claims about high-risk medical indications, such as . . . cancer or the likelihood of responding to a certain drug,” said Jeffrey Shuren, director of FDA’s Center for Devices and Radiological Health. Yet “in many cases the link between the genetic results” and the trait that some research claims they point to “has not been well-established,” putting consumers at risk of making decisions that could endanger their health.⁵⁶

Meanwhile, the University of California, Berkeley, and Stanford came under fire for new programs that invited some students to submit DNA for analysis. At Berkeley, incoming freshmen and transfer students were told they could send samples to be tested for genes linked to the ability to metabolize alcohol, the milk sugar lactose and folates — B vitamins important to cell growth and reproduction. Once school started, students could see their results and attend optional lectures and discussions about genetic testing. At Stanford, a new genetics class made up of medical and graduate students would have the opportunity to sequence and analyze their own genomes.⁵⁷

The schools argued that programs involving personal gene profiles would be the most effective motivators in getting students to seriously reflect on gene science and the ethical and other questions that personalized medicine may raise. Furthermore, because Stanford’s program is for people in pre-professional training, “it’s particularly important for these individuals to be adequately prepared” to analyze gene tests, said Keyan Salari, the Stanford program’s architect and director.⁵⁸

But some critics argue that neither students nor faculty nor the science of genetic testing are ready yet for such

initiatives. Especially in the Berkeley program, “I worry students won’t understand or would easily misconstrue the information they are being presented,” said Arthur L. Caplan, a professor of bioethics at the University of Pennsylvania. “They could have done it in a manner that was more sensitive to flaws in genetic testing.”⁵⁹

The National Collegiate Athletic Association (NCAA) debuted genetic screening of all Division 1 college athletes for sickle cell anemia in 2010. The dangerous genetic blood disorder, especially common among people of sub-Saharan African descent, can cause lethal complications after intense exercise even among people who carry the gene mutation but don’t show symptoms.⁶⁰

At least one young athlete, 19-year-old Dale Lloyd, a freshman at Rice University, died after a 2006 football practice apparently because he was unaware he had the mutated gene. Exercise-related sudden death is estimated to be 10 to 30 times higher among people with the mutation.⁶¹

Critics of the screening say that while it is well-intentioned, the program doesn’t have safeguards against false-positive test results; doesn’t provide for adequate counseling to help students understand the difference between carrying the gene and having the disease; could lead to unfairly banning students from athletics; and does nothing to make athletic practices safer, such as by reducing physical stress through proper hydration and cancellation of outdoor practice if heat and humidity are too high.⁶² ■

OUTLOOK

Statistical Uncertainties

As science reveals that all common diseases have multiple genetic and

environmental causes — with any single factor contributing only a small percentage of additional risk — it’s not clear how patients or physicians will cope with this finding, says Celeste Condit, a professor of communications at the University of Georgia.

“We tend to reason with a single-cause bias,” and that’s not surprising given the world humans evolved in, she says. “If a saber-tooth tiger was after you, you didn’t worry about the other risks that might be in the vicinity.” But “now we’re dealing with 10 percent of our disease risk coming from this factor, 20 percent from that, and it’s not clear how well we’ll deal with that situation.”

Putting gene-based diagnostics and therapies into clinical use will require extensive education for doctors, says genetics counselor Bernhardt. Physicians will need to become comfortable with ordering genetic tests and taking detailed family histories before prescribing treatments. “The doctors are going to be really struggling with this, particularly the older ones” who didn’t get much genetics education in medical school, Bernhardt says.

In a 2008 study researchers from the U.S. Department of Veterans Affairs and the RAND Health think tank found that primary-care physicians dubbed themselves “woefully underprepared” to incorporate such tasks into their practice, saying they lacked both the time and the knowledge to do so.⁶³

Genetics counselors will need to beef up their ranks and, especially, develop more efficient ways of working, Bernhardt says. In Idaho, for example, there are only two gene counselors.

Now that “every disease is a rare disease,” the National Institutes of Health should expand its efforts beyond basic research — preliminary scientific studies not directly transferable to clinical practice — into what’s called “translational” research, which figures out how to apply basic science to the development of drugs and other treatments, says Terry of the Genetics Alliance.

Up to now drug companies and other private-sector labs have done most translational studies because they could ultimately profit from providing the findings to patients. But the translational phase has long been called the “valley of death” for research because so many apparently promising ideas fail at this stage, Terry notes. So with the sale of blockbuster treatments to tens of millions of people increasingly unlikely, and genetic science reporting its first promising findings on rare single-gene diseases, the federal government must play a bigger role, she suggests. Under Obama-appointed NIH Director Collins, former chief of the Human Genome Project, that’s likely, Terry says.

A new NIH program, Therapeutics for Rare & Neglected Diseases (TREND), will help move “compounds that look particularly promising” as drugs “into the next phase of preclinical testing and animal toxicology,” Collins said early last year.⁶⁴

Progress from sequencing the genome to applying gene science to health is slower than many would like but is proceeding, says Dutta of the University of Virginia. “Ten years from now we’ll have a better understanding of our bodies, in 20 years we’ll better understand disease and in 30 years we’ll begin to have therapies.” ■

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About the Author



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FOR MORE INFORMATION

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Biotechnology Industry Organization, 1201 Maryland Ave., S.W., Ste. 900, Washington, DC 20024; (202) 962-9200; www.bio.org. Membership group advocating on behalf of companies involved in genetic technologies.

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Congress' nonpartisan auditing arm finds that current direct-to-consumer genetic testing companies provide misleading information on individual health risks that's of "little or no practical use."

"Personalized Medicine: Will It Work? Where Will It Take Us?" *The Hastings Center*, September/October 2010, www.thehastingscenter.org/Publications/HCR/Archive.aspx.

Analysts assembled by an independent, nonprofit research center examine social, ethical and policy issues related to genetic medicine's increasing "personalization" of health care. Among the issues explored: What happens when a patient's gene profile shows he or she will benefit only minimally from the only available treatment for a devastating illness? And is it appropriate for retail pharmacies to sell genetic test kits directly to consumers?

The Next Step:

Additional Articles from Current Periodicals

Consumer Tests

Darcé, Keith, "Genetic Tests on Shelves," *San Diego Union-Tribune*, May 11, 2010, p. A1.

Medical experts say consumers shouldn't conduct over-the-counter genetic tests without the direct supervision of a doctor who can interpret the results.

Graham, Judith, "Tests Go Under the Microscope," *Chicago Tribune*, June 15, 2010, p. A4.

The Food and Drug Administration says at-home genetic kits need to be regulated.

Japsen, Bruce, and Sandra M. Jones, "Walgreens Shelves Its Plan to Sell Genetic Kit," *Chicago Tribune*, May 13, 2010, p. A23.

Walgreens has reversed its decision to sell genetic kits made by Pathway Genomics following an FDA investigation into the supplier and product.

Lamb, Gregory M., "How Reliable Is Personal DNA Testing?" *The Christian Science Monitor*, Sept. 15, 2010.

Faulty interpretation and incomplete genetic research have been cited in criticism of direct-to-consumer tests.

Diseases

Allen, Elizabeth, "Study of Role Genes Play in Disease Advances," *San Antonio Express-News*, April 1, 2010, p. 5B.

Decreasing costs of sequencing a personal genome will help researchers better understand which genes influence specific diseases.

Kolata, Gina, "Muscle Disease Traced to Revived 'Dead Gene,'" *The New York Times*, Aug. 20, 2010, p. A1.

Geneticists report that one of the most common forms of muscular dystrophy is attributable to "dead genes" — or junk DNA — whose functions are largely unknown.

Tasker, Fred, "University of Miami Researchers ID Alzheimer's Risk Gene," *Miami Herald*, April 14, 2010.

University of Miami researchers have identified a gene that appears to double the risk of late-onset Alzheimer's disease.

Gene Mapping

Berger, Eric, "One Man's Quest Opens New Era of Genetic Medicine," *Houston Chronicle*, March 11, 2010, p. A1.

A researcher at Baylor University had his genome mapped to establish the cause of his own relatively rare nerve disorder.

Cheng, Maria, "DNA Mapping Enters New Territory," *Los Angeles Times*, May 2, 2010, p. A14.

The increasing availability of gene scans has raised medical and privacy concerns.

Maugh II, Thomas H., "A Leap in Mapping Genetic Variants," *Los Angeles Times*, Oct. 28, 2010, p. A23.

Researchers have identified 95 percent of the places in the human genome where individual traits are stored.

Wade, Nicholas, "A Decade Later, Gene Map Yields Few New Cures," *The New York Times*, June 13, 2010, p. A1.

Ten years after the first draft of the human genome was completed, medicine has yet to see much of the promised benefit.

Patents

"Utah Firm Makes Appeal in Federal Gene Patent Case," *The Associated Press*, Oct. 25, 2010.

The molecular diagnostics firm Myriad Genetics has asked a federal appeals court to decide whether the federal government can issue patents for naturally occurring genes.

Borrell, Brendan, "Patent Pending," *Los Angeles Times*, April 12, 2010, p. E3.

Some companies hold monopolies on interpreting information contained in patented genes they license, leaving many to wonder whether this benefits patients.

Marcus, Amy Dockser, "Study Faults Gene Licenses," *The Wall Street Journal*, April 15, 2010, p. A3.

The practice of granting exclusive licenses on individual genes could impede efforts to pinpoint disease risks, according to a Duke University study.

Salzberg, Steven L., "No One Should Have a Patent on Your Genes," *The Baltimore Sun*, Nov. 10, 2010, p. 19A.

Gene patenting has impeded several opportunities for promising biomedical research.

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Jost, Kenneth. "Rethinking the Death Penalty." *CQ Researcher* 16 Nov. 2001: 945-68.

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